ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1996, p. 2209–2211 Vol. 40, No. 9
0066-4804/96/$04.00+0

Once-Daily Aminoglycoside Therapy: Potential Ototoxicity

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Received 8 November 1995/Returned for modification 14 February 1996/Accepted 19 June 1996

Current data indicate that once-daily aminoglycoside therapy is as efficacious as traditional multiple daily dosing and equally or less toxic. Our experience with once-daily gentamicin, 6 mg/kg of body weight, led to a 10% (3 of 33 patients) occurrence of documented ototoxicity after prolonged aminoglycoside exposure.

Many studies have been performed to define optimal serum aminoglycoside concentrations and dosing regimens and the causes of their associated nephro- and ototoxicity (1). However, dosing regimens leading to maximum efficacy and minimal toxicity have not been clearly delineated. Recently, there has been a plethora of literature reporting increased efficacy and less toxicity associated with less-frequent (once-daily) aminoglycoside dosing compared to multiple-daily-dosing regimens (5, 6, 9–11). Current available data indicate that once-daily aminoglycoside dosing is equal in efficacy to the multiple-dosing regimen and the occurrence of nephrotoxicity is equal to or lower than that with the multiple-dosing regimen. However, there are limited data regarding the impact of this dosing regimen on the development of ototoxicity. We present three patients who developed ototoxicity after receiving once-daily gentamicin at 6 mg/kg of body weight per day according to a protocol designed to achieve peak concentrations in serum between 15 and 24 mg/liter and trough concentrations less than 0.5 mg/liter.

Patient 1. Patient 1 was a 52-year-old, 60-kg female with a history of calcinosis cutis, Raynaud's phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia syndrome for 5 years. She had nonhealing ulcers on the dorsa of both feet and was admitted to the hospital for excision of the exposed metatarsal heads. A bone culture grew *Pseudomonas aeruginosa*. The patient was started on ticarcillin-clavulanic acid (3.1 g every 4 h) and gentamicin (360 mg every 24 h). With this patient's calculated creatinine clearance of 71 ml/min, a steady-state peak gentamicin level of 18 mg/liter and trough of 0.02 mg/liter were expected. The patient's reported initial peak and trough gentamicin concentrations were 16 and less than 0.5 mg/liter, respectively. The patient was discharged home on the above medications without any complaints. Three weeks later, she was readmitted with a diagnosis of diverticulitis. She continued to receive gentamicin, but the dose was reduced to 280 mg every 24 h because a subsequent peak gentamicin level was 27 mg/liter. On 280 mg every 24 h, the gentamicin peak concentration was 18 mg/liter. When she was discharged, the gentamicin was inadvertently discontinued for 9 days.

Gentamicin, 280 mg every 24 h, was then reinstituted. Three days later the patient complained of dizziness, light-headedness, and difficulty walking which she had been experiencing since discharge. Gentamicin was discontinued. An audiogram was normal, but the patient was unable to stand up in a dark room. An ear, nose, and throat physician felt she had oscillopsia indicating bilateral labyrinthine dysfunction. Further evaluation 6 weeks later demonstrated some difficulty with oculomotor tasks. There was no positional or spontaneous nystagmus. Cool-water irrigation produced very slight nystagmus. Ice water irrigation produced a weak response in both ears suggesting bilateral labyrinthine hypoactivity.

Patient 2. Patient 2 was a 71-year-old, 72-kg male admitted with a temperature of 103°F (ca. 39.4°C), rigors, difficulty urinating for 3 days, and right back pain radiating to his scrotum and right leg. Magnetic resonance imaging of the spine revealed discitis at L3-L4, and a bone scan was positive for vertebral osteomyelitis. Blood cultures from admission grew *Enterobacter aerogenes*, and the patient was placed on imipenem-cilastatin (500 mg every 6 h) and gentamicin (430 mg [6 mg/kg] every 24 h). He had a calculated creatinine clearance of 72 ml/min. Initial gentamicin peak, 12-h, and trough levels were 18, 1.1, and 0.5 mg/liter, respectively, which were close to an expected peak of 20 mg/liter and trough of 0.1 mg/liter. After 10 days of therapy, repeat peak and trough levels were 15 and 1.6 mg/liter, respectively. Because of an increase in serum creatinine (1 to 1.3 mg/dl), the dose was adjusted to 430 mg every 36 h for an additional 7 days. Because of an elevated peak gentamicin level of 32 mg/liter (trough = 1.1 mg/liter), the dose was further reduced to 400 mg every 36 h, which the patient received for an additional 11 days. The patient's serum creatinine returned to baseline.

After receiving 40 days of therapy, the patient complained of dizziness while ambulating, and during a physical therapy exam the patient was noted to have increased unsteadiness. The patient noted that he had been feeling dizzy while in the hospital. After discharge, he used a cane to walk most of the time. He described his unsteadiness as a sensation of being drunk and feeling as though the room were spinning. Magnetic resonance imaging of the brain and brain auditory evoked response were normal.

Electronystagmogram revealed mild left nystagmus in the right and left lateral positions. Ice water calorics showed markedly reduced responses in both ears consistent with ototoxicity. A computerized rocking chair test indicated a partially decompensated peripheral vestibular disorder with good central suppression. Audiometry revealed a bilateral moderate to severe sensorineural hearing deficit.

Patient 3. Patient 3 was an 80-year-old, 70-kg male who developed the sudden onset of midabdominal pain, nausea, fever, and chills. He was hypotensive on admission with a blood pressure of 80/50 mm Hg. Physical examination revealed mild epigastric tenderness. An endoscopic retrograde cholangiopancreatography revealed a stone blocking the bile duct, and a

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stent was placed. Blood cultures from admission grew *Escherichia coli*. Bile cultures grew *E. coli*, *P. aeruginosa*, *Enterococcus faecium*, and *Pseudomonas putida*. The patient was treated with imipenem-cilastatin (500 mg every 6 h) and gentamicin (420 mg [6 mg/kg] every 24 h) on the basis of a calculated creatinine clearance of 57 ml/min. While initial steady-state gentamicin peak and trough concentrations were expected to be 20 and 0.25 mg/liter, respectively, the actual peak was 15 mg/liter, the 12-h level was 3.3 mg/liter, and the trough was 0.7 mg/liter. Based upon pharmacokinetic calculations, these gentamicin levels indicate that the patient had an increased volume of distribution. However, the clearance was not different from that estimated. Following 12 days of therapy, the patient's estimated creatinine clearance decreased to 44 ml/min and subsequent gentamicin levels were a peak of 19 mg/liter and trough of 1.3 mg/liter. The patient received a total of 16 days of therapy. He was discharged from the hospital feeling well and had no vestibular complaints. After being off gentamicin for 2 weeks, he developed some dizziness and felt unsteady. An electronystagmogram revealed normal caloric responses in both ears but unilateral right-side weakness consistent with a peripheral vestibular neuropathy. Magnetic resonance imaging of the brain was normal. An audiogram revealed mild to moderate sensorineural hearing loss from 500 to 8,000 Hz (low and high frequencies) in the right ear along with poor speech discrimination; the left ear had a mild to moderate high-frequency hearing loss (3,000 to 8,000 Hz) and excellent speech discrimination.

Aminoglycoside antibiotics have been shown to produce ototoxicity which may be irreversible in both humans and experimental animals (2). Ototoxicity can take the form of auditory and/or vestibular changes resulting in destruction of sensory hair cells in the cochlea and vestibular labyrinth (2). The initial stages of auditory toxicity involve selective destruction of the outer hair cells of the organ of Corti. In this early stage of toxicity, the damage is usually limited to higher frequency levels (4,000 to 8,000 Hz) and does not affect frequencies utilized in conversational hearing (4). The toxic changes are generally reversible at this stage. If the insult is allowed to progress, the inner hair cells of the cochlear apex become damaged (12). Hearing impairment then occurs at lower frequencies, and conversational hearing is compromised. At this later stage, the deficit is generally permanent or only partially reversible. Vestibular toxicity generally parallels cochlear damage and is usually manifested by vertigo, nausea, dizziness, and nystagmus (12).

The precise mechanism of hair cell destruction in both forms of ototoxicity is unclear. The incidence of hearing loss ranges from 2 to 25% (7). This wide range may be due in part to the lack of baseline and subsequent auditory determinations and to the absence of a universally accepted standard for defining drug-induced ototoxicity. In addition, because the vast majority of patients receiving aminoglycoside therapy are lost to follow-up and the symptoms are ambiguous, the permanent or transient nature of such an adverse reaction is also not known. Several factors have been associated with a higher incidence of ototoxicity, including (i) duration of therapy (>8 days), (ii) cumulative dose, (iii) total daily dose, (iv) peak and trough serum drug concentrations, (v) concurrent diuretic therapy, (vi) underlying disease states, (vii) previous exposure to aminoglycoside therapy, (viii) increased age, and (ix) specific aminoglycosides (7, 12). However, recently it has been suggested that the accumulation of aminoglycosides in cochlear and vestibular tissues is related to prolonged exposure rather than to transient high concentrations in serum (3). Therefore, prolonged exposure of the hair cells to the aminoglycoside may account for the damage observed (3).

Studies evaluating once-daily aminoglycoside dosing have suggested that the incidence of ototoxicity is similar to or less than that with traditional dosing of aminoglycosides (3). However, many studies did not evaluate hearing, used various methods to establish ototoxicity, or used various doses (range, 3.8 to 7 mg/kg/day) or patients were on short courses of aminoglycoside therapy (3, 8). In one large prospective study evaluating over 2,000 patients receiving once-daily aminoglycoside dosing (7 mg/kg/day), the average length of therapy was only 4.5 days (8). Only 808 (37%) patients received 6 or more days of therapy. However, one patient developed residual ototoxicity after receiving 5 weeks of therapy. Patients were followed up clinically, and determination of ototoxicity was made on the basis of patient interviews and physical examinations.

All three patients that we report on received aggressive once-daily dosing of an aminoglycoside for a period of 2 weeks or greater (range, 16 to 40 days). Despite two patients' initial serum drug concentrations being within the guidelines for dosing once-daily aminoglycosides (defined by Nicolau et al. [8]), the total daily doses used in these three patients were higher than conventional dosing guidelines for patients with some degree of renal impairment. Because of the small number of patients, we cannot determine if the observed ototoxicity was due to the dose or prolonged exposure to the drug. We have rarely observed similar ototoxicity in patients receiving conventional dosing of aminoglycosides, even when prolonged therapy is administered. However, upon initiating once-daily aminoglycoside dosing in our institution, 3 of 33 patients (10%) developed aminoglycoside-induced ototoxicity within a 3-month period. The high incidence of this adverse effect may be related to the duration of aminoglycoside therapy, the aggressive high-dose regimen, or both. Consequently, we recommend that prudence be employed in using this new aggressive dosing regimen. In addition, dosage adjustments may be required, and practitioners should pay particular attention to the development of ototoxicity. This may be especially important in patients receiving high doses and prolonged courses of aminoglycoside therapy.

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